LETTER TO THE EDITOR

A proposal of warning signs for primary immunodeficiencies in the first year of life

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Editor,

As primary immunodeficiencies (PIDs) represent a heterogeneous group of more than 180 defects (1), early diagnosis is, indeed, a challenge, and PIDs are still detected too late throughout the world. Awareness among pediatricians and family doctors is critical for early recognition and treatment. Thus, the 10 warning signs of the Jeffrey Modell Foundation (http://www.info4pi.org) have facilitated PID identification, mainly in children and young adults with antibody deficiencies. However, the most severe PIDs manifest very early in life, and most are considered pediatric emergencies that require hematopoietic stem cell transplantation, as the groups listed below (a–f). Their most common feature is high susceptibility to infections, but several PIDs cause immunedysregulation, with manifestations of autoimmunity, excessive inflammation and/or allergy.

(a) Severe combined immunodeficiencies (SCID) include 15 different defects, some patients presenting as Omenn's syndrome (2, 3). A minimal prevalence estimation is 1:100,000 births, but experts believe that it is at least two-fold more (4).

(b) Familial hemophagocytic lymphohistiocytosis (HLH) includes several genetic defects, with an estimated prevalence of 1:50,000 births (5);

(c) Immune-dysregulation-polyendocrinopathy-enteropathy-X-linked-syndrome (IPEX) results from lack of Treg cells (6), with around 100 cases published.

(d) Severe phagocyte disorders, such as leukocyte adhesion deficiencies (LAD), severe congenital neutropenia, chronic granulomatous disease (CGD) and defects of innate immunity, such as NEMO, IRAK4 and MyΔ88 deficiencies (1).

(e) DiGeorge syndrome (DGS), associated with 22q11.2 deletion, presents a prevalence of 1:3000–4000 births (7).

(f) Wiskott–Aldrich syndrome (WAS), with around 600 cases described.

Based on extensive literature review and compilation of our 30-year-long experience, we propose 12 warning signs of PIDs in infants. Besides clinical signs, accessible and low-cost examinations were incorporated.

1 Severe and/or persistent fungal, viral or bacterial infections. Fungal (mainly thrush and *Pneumocystis jiroveci* pneumonia) and viral infections (including RSV) are the most frequent initial SCID manifestations (2, 4), while disseminated or deep-seated bacterial infections can be early manifestations of neutrophil disorders, and innate immunity defects.

2 Adverse reaction to BCG vaccine has been observed in SCID, IL-12/IFN-gamma axis defects, NEMO deficiency, and CGΔ (1,2); adverse reactions to other live vaccines such as poliovirus and Rota virus were also associate with PIΔs.

3 Persistent diabetes mellitus or other autoimmune and/or inflammatory manifestation may be a precocious feature of a PID with immunedysregulation, mainly IPEX (6). Severe inflammatory manifestation in a baby makes one consider auto-inflammatory disease.

4 Sepsis-like clinical picture without microbial detection should be strongly suggestive of HLH diagnosis (5). Pyogenic lesions without germ isolation should indicate an auto-inflammatory disease.

5 Persistent diarrhea is observed in most babies with SCID and IPEX (2, 6).

6 Extensive skin lesions are seen in all Omenn's syndrome, WAS and graft-versus-host reaction cases, and in most IPEX (1,2).

7 Congenital heart defects (mainly conotruncal anomalies) are observed in 75% of patients with DGS (7). 22q11.2 deletion was observed in around 5% of patients with congenital cardiac defects.

8 Delayed cord detachment (> 30 days) is a typical LAD sign but has also been described in innate immunity defects characterized by impaired inflammatory reaction.

Table 1 The 12 warning signs of primary immunodeficiency (PID) in the first year of life

1. Severe and/or persistent fungal, viral, or bacterial infections
2. Adverse reaction to Live vaccine specially BCG
3. Persistent diabetes mellitus or other autoimmune and/or inflammatory manifestation
4. Sepsis-like clinical picture without microbial isolation
5. Extensive skin lesions
6. Persistent diarrhea
7. Congenital heart defects (mainly conotruncal anomalies)
8. Delayed umbilical cord detachment (>30 days)
9. Familial history of PID or early deaths caused by infection
10. Persistent lymphocytopenia 2,500 cells/mm^3 or other cytopenia, or leukocytosis without infection
11. Hypocalcemia with or without seizures
12. Absence of thymic shadow at X-Ray

9 Familial history of a PID or early deaths caused by infection.

10 Persistent lymphocytopenia or other cytopenia, or leukocytosis without infection. Data from white blood cell counts are useful in early detection of PIDs: (i)lymphocytopenia (< 2500 cells/mm^3) (2) is seen in most SCID; (ii)neutropenia 1,000 cells/mm^3 is indicative of Kostmann's syndrome; (iii)pancytopenia or bicytopenia in an infant with sepsis-like picture is strongly suggestive of HLH; (iv)thrombocytopenia is seen in WAS but can also be an auto-immune phenomenon, as in IPEX; (v)leukocytosis without infection ($> 30{,}000$ cells/mm^3) is seen in LADs.

11 Hypocalcemia with or without seizures was observed in up to 60% of patients with DGS.

12 Absence of thymic shadow in chest X-ray is a sign of SCID or DGS.

Currently, there are US efforts to include SCID in universal neonatal screening programs, being T-cell receptor excision circles (TRECs) measurement, the most promising test (4, 8). Nevertheless, several severe PIDs (HLH, IPEX, and neutrophil disorders) should not be associated with low TRECs, and the refinement of clinical detection continues being crucial for precocious diagnosis.

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